Working Title: MIGRAINE PREVENTIVE TREATMENT AND ITS INFLUENCE ON THE CHANGE IN THERAPEUTIC INTENSITY WITH DISEASE-SPECIFIC ABORTIVE AGENTS

ABSTRACT

Objective: To (1) examine prescribing patterns of migraine-specific abortive medication among new users and non-users of migraine preventive therapy and (2) determine if treatment with a migraine preventive agent influences the utilization of migraine-specific abortive agents.

Methods: This retrospective, longitudinal cohort study examined medical and pharmacy claims data among beneficiaries with migraine in the Military Health System from 1 October 2002 and 30 September 2004. All patients between 17- 64 years of age with migraine were selected if they received at least one prescription for a migraine-specific abortive agent between 1 April 2003 and 30 September 2003 (the index prescription). Patients were further classified into cohorts of new users and non users of migraine preventive treatment. The analysis examined the change in utilization of migraine-specific abortive agents in Defined Daily Doses among the two study cohorts using matching adjusted difference-in-differences estimation.

Results: A total of 2,673 patients met study inclusion criteria with 750 participants (28%) classified as new users of migraine preventive treatment and 1,923 participants (72%) identified as a non-equivalent comparison group. Without exception, rates of migraine-specific abortive medication were higher among users of migraine preventive treatment. The estimates derived after stratification and nearest neighbor matching suggest that migraine preventive treatment was associated with an average decline in

migraine-specific abortive medication of 9.2 ($p < 0.01$) and 6.4 ($p = 0.054$) Defined Daily Doses, respectively.

Conclusions: The results indicate that treatment with a migraine preventive agent is associated with a modest reduction in use of migraine-specific abortive medication relative to a similar group of non-users over the same time interval in the Military Health System.

Disclaimer: The thoughts and opinions expressed in this paper are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the United States Government.

INTRODUCTION

Migraine is a widespread and disabling condition affecting people during the most productive years of life.[1-2] The preferred management strategy for patients with moderate-to-severe headache is treatment with a migraine-specific abortive medication (MSAM) designed to counteract the specific physiologic changes thought to occur during an attack.[3] Successful treatment provides symptomatic relief of the headache allowing a return to normal function. Despite availability of effective abortive medication, several problems with this treatment have been identified. Research has shown that inappropriate use of MSAM can occur. If left uncorrected, inappropriate use could lead to unintended negative consequences.[4] For example, excessive use of MSAM can produce a rebound phenomenon that worsens an individual's headaches.

Another important consideration is the high cost of MSAM treatment. This is particularly true for the newest class of agents known as the serotonin receptor agonists or the "triptans" as they are commonly referred. In 1998, Hu and colleagues[5] estimated that the total cost of direct care consumed in the treatment of migraine was 1.2 billion dollars. In 2003, GlaxoSmithKline reported that United States sales for sumatriptan (Imitrex®), one of the seven triptans currently available in the U.S. market, at 1.3 billion dollars. Excluding inflation, the cost of just one prescription medication used primarily for the treatment of migraine exceeded the estimated total cost of all migraine-related care provided in the U.S. just five years earlier.

Given these concerns, additional research should evaluate how other treatments augment migraine-specific abortive therapy. For instance, it is currently uncertain what impact, if any, migraine prevention has on MSAM utilization. Clinical evidence would

suggest that migraine preventive treatment can reduce the frequency and severity of headaches. But, does this reduction manifest itself as a decline in the use of abortive treatments? If the use of MSAM could be reduced without sacrificing an individual's quality-of-life, it could be beneficial to both the patient and the health care system.

OBJECTIVE

The specific objectives of this study were to: (1) examine prescribing patterns of migraine-specific abortive medication among new users and non-users of migraine preventive treatment and (2) determine if treatment with a migraine preventive agent influences the utilization of migraine-specific abortive medication.

METHODS

We conducted a retrospective longitudinal analysis of pharmacy and medical claims data among beneficiaries suffering from migraine in the Military Health System (MHS). Two years of data were available for the analysis beginning 1 October 2002 and ending 30 September 2004. Our initial patient population and study cohorts were derived using a claims-based algorithm summarized in Figure 1. The two cohorts depicted in Figure 1 represented the study sample from which the analysis was conducted and all inferences are made. Medications classified as abortive and as preventive are summarized in Tables 1 and 2 accordingly.

The independent variable was a dichotomous measure of whether or not an individual received preventive treatment (1 = preventive cohort and 0 = comparison cohort). The dependent variable was characterized by the use of MSAM measured in Defined Daily Doses (DDD) providing a estimate of abortive therapeutic intensity. A single DDD represented the usual dose required for treatment when taken by an adult for

the primary indication and provided a common unit of measurement to compare of various drug doses and dosage forms.[6-8] Table 1 lists the strength of one DDD for each MSAM included in this study. Each patient's utilization patterns were defined for three sequential six month intervals beginning six months before the study index date and ending 12 months after. The intervals were referred to as pre-treatment, transitional (because it was during this period that migraine preventive treatment was initiated in the treatment cohort), and post-treatment respectively.

Due to the longitudinal nature of our data, we adopted the following strategy. We calculated the change in therapeutic intensity of MSAM use (in DDD) between the post-treatment and transitional phase for both the treatment and the comparison group. In turn, each measure of change for the two groups was differenced providing an unadjusted estimate of the average treatment effect on the treated participants. This procedure is commonly referred to as a difference-in-differences (DiD) estimator and allows an examination of preventive treatment and its association with any differential change in MSAM utilization.

To account for pre-treatment differences between groups, we repeated the DiD analysis on a subset of participants matched on pre-treatment characteristics using a propensity score method.[9] Recent research has shown that a combination of matching and double difference estimation outperform other commonly used matching estimators.[10,11] Each pre-treatment variable used in the matching procedure is summarized in Table 3 and was included because of a hypothesized potential to influence the study focal relationship between preventive treatment and the change in migraine-specific abortive medication use. Interaction terms (e.g., quadratic terms) were included

to allow for non-linear effects on the dependent variable and potential heterogeneity among study control variables. After derivation of the propensity score, we estimated two measures of the average treatment effect over the region of common support using stratification and nearest neighbor matching (with replacement). All analyses were conducted with of Stata, 8.0 (Stata Corporation, College Station, Texas).

RESULTS

The study sample consisted of 2,673 participants, the majority of whom were female in their early thirties identified as non-active duty beneficiaries. All major branches of military service were proportionately represented with the majority of individuals assigned in geographic regions across the continental United States and just under 13% stationed overseas. The larger proportion of patients were assigned to Military Treatment Facilities (MTF) classified as hospitals (i.e., provide inpatient services and typically possess a wider array of specialties) while the remaining 46% were assigned to MTF classified as clinics (i.e., smaller facility intended to provide emergent and ambulatory care only). Fifty-one percent of study subjects used both retail and military pharmacy services and just over 30 percent received specialty care from a neurologist during the pre-treatment window.

After separating the sample into groups based on use of a migraine preventive agent, the treatment cohort included 750 patients (28%) and the comparison group had 1,923 patients (72%). The patterns of MSAM use are depicted graphically in Figure 2. Utilization has been aligned in "60 day" intervals according to each patient's index date and represents the number of DDD dispensed per person during each 60 day interval. The figure shows that average utilization of MSAM was consistently higher among the

treated patients in contrast to the untreated comparison group. Both cohorts experienced an increase in utilization during the transition phase (60 day intervals 1, 2 and 3 from Figure 2) that declined steadily during the remainder of the study. The post-index date change in rates of utilization among the treatment group appears to decline at a faster rate than utilization among the comparison group during the same timeframe.

The results from our simple unadjusted difference-in-differences estimate are depicted in Table 4. The treatment cohort experienced an average reduction in abortive utilization of 9.8 DDD during the post-treatment period relative to the comparison group ($p < 0.01$). Despite the significant result, the model does not make allowances for any other sources of variation such as pre-treatment differences between the two study cohorts.

To investigate the extent of pre-treatment differences, we examined the distribution of all observed patient characteristics after stratification on cohort membership using standardized percent differences. As shown in Table 5, moderate to large differences existed between study cohorts on several important characteristics. For example, the likelihood of receiving pre-treatment specialty care differed significantly among the two groups. In this case, a much larger proportion of treated patients received care from a neurologist than did patients from the comparison group. If provision of pre-treatment specialty care is associated with the probability of receiving migraine prevention and the utilization of a migraine-specific abortive medication, it could confound the observed association from our unadjusted model in Table 4.

In an effort to control for the group differences displayed in Table 5, we estimated the propensity score (i.e., the conditional probability of receiving treatment given the

observed variables) for all pre-treatment characteristics in Table 3. After score generation, we tested the balancing hypothesis which compared the means of each characteristic for differences between the two cohorts based on strata of the propensity score. The test was satisfied for our propensity score specification at an alpha of 0.01. Using two alternate forms of matching, we recomputed difference-in-differences model matched on pre-treatment characteristics.

The results illustrated in Table 6 are similar to the unadjusted comparison reported earlier (Table 4). Although, the matching process generates more conservative results, the qualitative conclusions remain unchanged. Nearest neighbor matching gave the most conservative estimate of the average reduction in MSAM use during the post-treatment period. The estimate implies that the average effect of treatment on the treated was a reduction in MSAM use of 6.4 DDD relative to the comparison group.

DISCUSSION

This study provided information on two important questions related to the management of migraine headache. First, it highlights the extent of MSAM use among patients with migraine headache in the MHS. Without exception, patients classified as new users of migraine preventive treatment received more abortive medication than did the comparison group. This was not surprising result. One would expect that patients with more severe disease would be better candidates for preventive treatment and use more abortive medication. This conclusion could prove useful for researchers and health policy makers interested in population measures of disease severity. This is particularly true for migraine because many of the clinical features are subjective making it difficult to assess patient progress without direct access to the patient or the medical record.

Second, the study demonstrated a modest association between migraine prevention and the evolution of MSAM use in the year following treatment. Using our most conservative estimate suggests that treatment with a migraine preventive agent was associated with an average decrease of 6.4 DDD over a six month period relative to the untreated comparison group over the same interval. Although statistically significant, it is difficult to argue that the results suggest overwhelming economic benefits due to a reduction in MSAM use. In our study, the average prescription quantity for a MSAM was 12.2 DDD at an average cost of $102. If our results could be extended to one year, patients undergoing treatment would experience an average reduction of slightly more than one prescription annually. While it is unlikely to offset the cost of treatment with the preventive agent over that same year, it adds an additional incentive to the already established benefits of migraine prevention.

The research should be considered in context of its limitations. All normal shortcomings of observational data apply. Furthermore, several statistical weaknesses should be considered. We employed a change score as our dependent variable and compared the rate of change between the treatment and comparison group as the outcome of interest. This approach relies on several assumptions for unbiased estimation. The most important of which requires the absence of time variant fluctuation among characteristics associated with treatment assignment. In other words, we assume that control subjects experience the same rate of change that the treatment participants would have experienced in the absence of treatment. If this does not hold, then the estimated effects are biased.

In conclusion, we identified patterns of migraine-specific abortive medication use among new users and non users of migraine preventive therapy. Patients undergoing prevention were, on average, higher users of abortive treatment throughout the study. In addition, we detected a statistically significant association suggesting that abortive medication use in the treatment group declined at a steeper rate than did abortive use in an untreated comparison group. However, the economic significance of this finding is debatable. Additional research should examine the performance of individual migraine preventive agents and evaluate the importance of prevention adherence on utilization of migraine-specific abortive treatments.

REFERENCES

1. Lipton RB, Scher AI, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology 2002;58:885-94.

2. Lipton RB, Diamond S, et al. Migraine diagnosis and treatment: results from the American Migraine Study II. Headache 2001;41:638-45.

3. Silberstein S. Practice parameter: Evidence-based guidelines for migraine headache. Neurology 2000;55:754-763.

4. Gaist D, Hallas J, et al. Is overuse of sumatriptan a problem? A population-based study. Eur J Clin Pharmacol 1996;50:161-65.

5. Hu XH, Markson LE, et al. Burden of migraine in the United States. Arch Intern Med 1999;159:813-18.

6. Dukes MN. Drug utilization studies. Methods and uses. Introduction. WHO Regional Publications 1993;45:1-4.

7. WHO Collaborating Centre for Drug Statistics Methodology ATC index with DDDs. Oslo, Norway. Available: http://www.whocc.no/atcddd/publications.html#3 .

8. WHO Collaborating Centre for Drug Statistics Methodology ATC classification and DDD assignment. Available: http://www.whocc.no/atcddd/publications.html#2 .

9. Rosenbaum, P. R., and Rubin, D. B. (1983). "The central role of the propensity score in observational studies for causal effects," Biometrika 70: 41-55.

10. Heckman JJ, Ichimura H, and Todd PE. Matching as an econometric evaluation estimator: evidence from evaluating a job training programme. Rev Econ Stud 1997;64:605-54.

11. Blundell R, and Dias MC. Evaluation methods for non-experimental data. Fisc Stud 2000;21:427-68.

TABLE 1. Defined Daily Dose Comparison of Migraine-Specific Abortive Medication

5-HT$_1$ Receptor Agonist	*Dosage Form*	*Defined Daily Dose*
almotriptan (Axert®)	tablets	12.5 mg
dihydroergotamine (D.H.E. 45®)	injection	4 mg
dihydroergotamine (Migranal®)	nasal spray	1 mg
eletriptan (Relpax®)	tablets	40 mg
ergotamine (single ingredient)	any route	4 mg
ergotamine (combination product)	any route	2 mg
frovatriptan (Frova®)	tablets	2.5 mg
isometheptene (combination product)†	capsules	5 capsules
naratriptan (Amerge®)	tablets	2.5 mg
rizatriptan (Maxalt®, Maxalt-MLT®)	tablets	10 mg
sumatriptan (Imitrex®)	tablets	50 mg
sumatriptan (Imitrex®)	nasal spray	20 mg
sumatriptan (Imitrex®)	injection	6 mg
zolmitriptan (Zomig®)	tablets	2.5 mg

† Isometheptene products are not included in the Anatomical Therapeutic Classification used to assign Defined Daily Doses by the World Health Organization. Instead, isometheptene products were assigned a conservative definition of a DDD that reflects the maximum recommended amount of medication used to treat one migraine headache in a twelve hour period.

TABLE 2. Evidenced-Based Treatments for Migraine Prevention Selected by the American Academy of Neurology

Migraine Preventive Medications
amitriptyline
atenolol
divalproex sodium
fluoxetine
gabapentin
guanfacine
metoprolol
nadolol
nimodipine
propranolol
timolol
topiramate†
verapamil

† This product was not recognized as a first-line choice when the AAN guidelines were released in 2000. Since that time, topiramate received an FDA indication for migraine prevention and is now considered a primary option for headache prevention.

TABLE 3. Summary of Study Matching Variables

Matching (Control) Variables	*Variable Type*
Age	continuous (in years)
Age^2	continuous (in years)
Gender	dichotomous (1 = female, 0 = male)
Geographic region	categorical (corresponding Tricare region)
Place of care	dichotomous (1 = outside MTF, 0 = in MTF)
Age * Gender	interaction term between age & gender
Beneficiary Category	dichotomous (1 = active duty, 0 = other)
Bencat * Gender	interaction term between beneficiary category & gender
Branch of Service	categorical (corresponding to uniformed service)
Location of Prescription Service	categorical (MTF pharmacy vs. non-MTF pharmacy)
Primary treatment facility	categorical (clinic, hospital, or teaching hospital)
Comorbidity Measure	continuous (number of unique medications prescribed)
Comorbidity $Measure^2$	continuous (number of unique medications prescribed)
Pre-treatment MSAM use	continuous (pre-index MSAM use in DDD)
Pre-treatment MSAM use^2	continuous (pre-index MSAM use in DDD)
Early Cohort Entry	dichotomous (1 = entry before median index date)
Specialist Care	dichotomous (y/n, specialist care during pre-treatment)

Table Abbreviations: Migraine-Specific Abortive Medication (MSAM); Defined Daily Dose (DDD); Military Treatment Facility (MTF)

TABLE 4. Bivariate Analysis Comparing Migraine-Specific Abortive Utilization for the Treatment and Comparison Cohorts

	Transition Period†	*Post-Treatment Period†*	*Difference (standard error)*
Treatment Cohort	42.2	29.8	-12.4 (3.0)***
Comparison Cohort	20.5	17.9	-2.6 (1.3)**
Difference-in-differences			-9.8 (2.5)***

Note: Each populated cell in the second and third column represent the average number of DDD dispensed per person over a 6 month interval.

†. Transition period represented the 180 days immediately following (but not including) the index date and the post-treatment period represented the 180 days following the transition period.

** $p < 0.05$

*** $p < 0.01$

TABLE 5. Sample Pre-Treatment Characteristics Stratified by Cohort Membership

Sample Mean Characteristics	*All Patients*		*Standardized Percent Difference(d_i)*
	Preventive	*No Preventive*	
# of patients	750	1,923	
Age	32.5	33.6	-11.0
Female (%)	75.5	80.9	-13.2
Beneficiary Category (%)			
Active Duty	40.1	34.2	12.3
Other	59.9	65.8	-12.3
Branch of Service (%)			
Army	32.8	33.5	-1.5
Air Force	28.3	30.4	-4.7
Navy/Marine	37.3	34.3	6.3
Other	1.6	1.9	-2.3
Geographic Region (%)			
Northeast	9.7	10.1	-1.3
Mid-Atlantic	20.3	18.6	4.3
Southeast	10.5	9.7	2.7
Gulf South	5.7	7.3	-6.5
Heartland	6.9	4.0	12.8
Southwest	8.5	8.9	-1.4
Central	14.1	16.1	-5.6
Southern California	5.7	6.3	-2.5
Golden Gate	2.4	1.7	5.0
Northwest	5.1	4.1	4.8
Overseas	10.9	13.2	-7.0
Treatment Facility (%)			
Clinic	36.3	50.5	-29.0
Hospital	25.9	22.2	8.6
Teaching Hospital	37.9	27.3	22.7
Source of Medical Care (%)			
Direct Care Only	47.2	53.3	-12.2
Some Purchased Care	52.8	46.7	12.2
Prescription Point of Service (%)			
MTF Only	41.5	51.8	-20.7
Low Retail	30.7	23.9	15.3
High Frequency Retail	27.8	24.3	8.0
Early Cohort Entry (%)	51.5	40.3	22.5
Pre-Index Migraine Abortive Use	28.5	24.8	7.7
Pre-Index Comorbidity	9.8	8.2	26.9
Pre-Index Specialty Care (%)	51.5	22.7	47.8

Note: Standardized percent difference (d_i) is equal to $100(X_t - X_c) / \sqrt{[(s^2_t + s^2_c)/2]}$ where X_t and X_c are the covariate means and s^2_t and s^2_c are the sample variances of the i^{th} covariate for the treatment and control groups respectively.

TABLE 6. Matching Adjusted Difference-in-Differences Estimate of the Average Treatment Effect Associated with Receiving Migraine Preventive Treatment

Matching Method	*Treated Participants*	*Comparison Participants*	*Measure of Effect (standard error)*	*t statistic*
Nearest Neighbor†	750	521	-6.4 (3.2)*	-1.929
Stratification‡	747	1921	-9.2 (2.8)**	-3.297

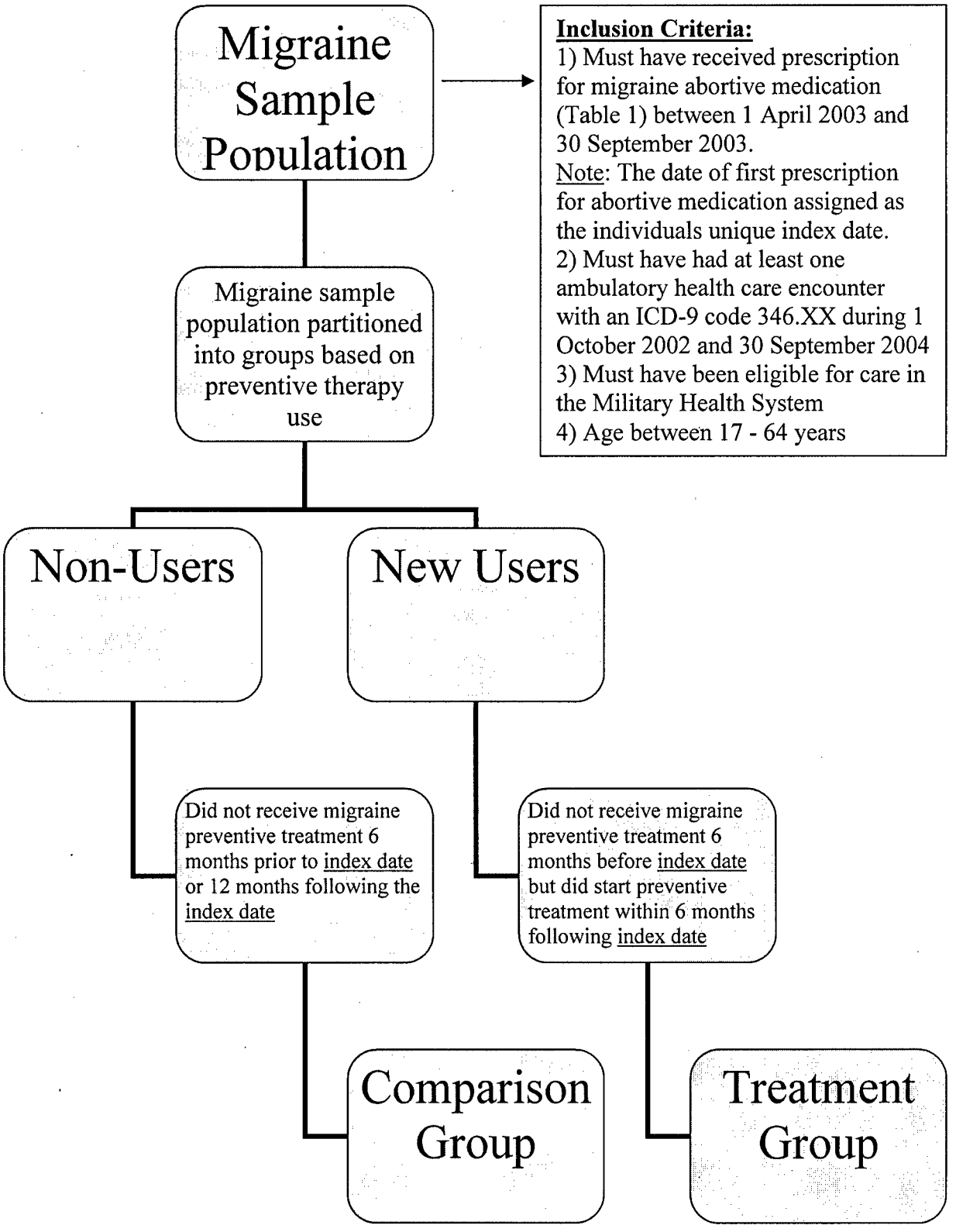
† Nearest neighbor matching was conducted with replacement. This means that comparison subjects were selected based on closest proximity in absolute terms to each treated subject. Thus, some comparison subjects matched with more than one treated participant leading to fewer matched comparison subjects.

‡ Matching via stratification excludes three treated participants because the eleventh strata of the propensity score contained only treated subjects. Hence, a pooled measure of effect cannot be calculated and the three treated subjects are excluded from the analysis.

* $p < 0.10$

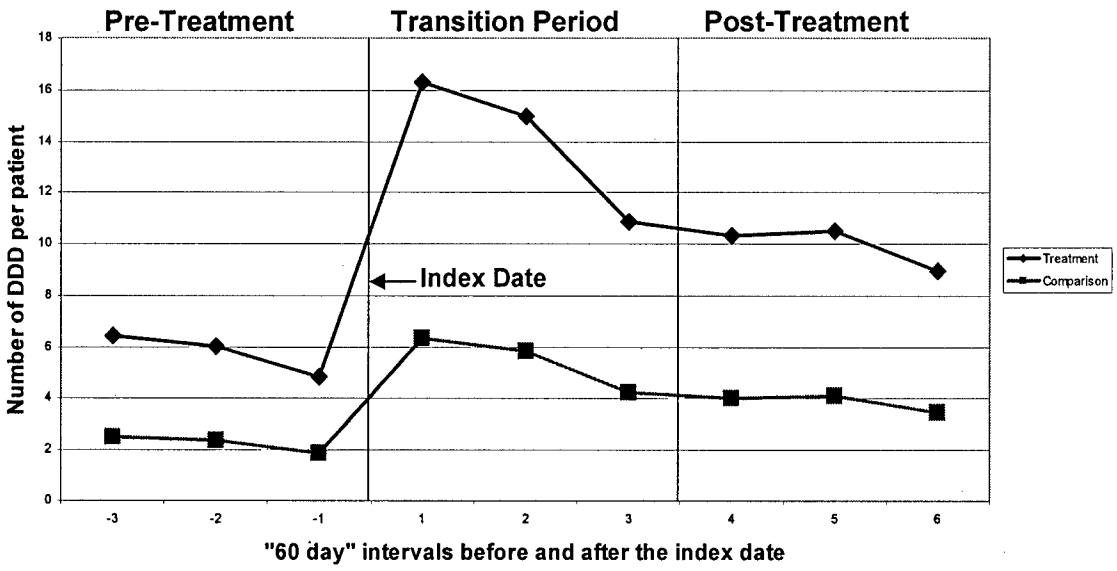
** $p < 0.05$

FIGURE 1. Flowchart for Sample Selection and Cohort Assignment



Note: Treatment refers to treatment with a migraine preventive agent (Table 2).

FIGURE 2. Unadjusted Rates of Migraine-Specific Abortive Medication Utilization During Study for New Users (Treatment) and Non Users (Comparison)



Note: The pre-treatment includes 180 days just prior to the index date. The transition period represents the 180 days immediately following the index date. The post-treatment period includes the 180 days following the transitional period.

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